## REMARKS

Claims 1-25 are pending in this application. By this amendment, Claims 11, 13, 16, 24 and 25 have been amended. Claim 18 has been canceled. No new matter has been added thereby. The Examiner's rejections are traversed below.

Claim Rejections Under 35 U.S.C. § 102

The Examiner has rejected all of the pending claims under 35 U.S.C. § 102(b) as anticipated by either Mitchell et al., U.S. Patent No. 5,462,946, or Golz-Berner et al., PCT Publication No. WO 99/66881 (using U.S. Patent No. 6,426,080 as an English equivalent). Claim 18 has been canceled. Applicant traverses these rejections with respect to Claims 1-17 and 19-25.

1. Mitchell, U.S. Pat. No. 5,462,946

The Examiner has rejected Claims 1-2, 6-10, 12-18, and 20-25 under 35 U.S.C. § 102(b) as being anticipated by Mitchell et al., U.S. Patent No. 5,462,946. The Examiner characterizes Mitchell in the following terms:

> Mitchell teaches pharmaceutical compositions and their methods of use, the compositions contain nitroxide compounds (including TEMPOL) that can be used as radiation protectants for skin mucositous and hair loss (also known as alopecia), which can be applied as an ointment, lotion, or cream (satisfying the claim for a gel or thickened liquid) and intravenously or orally by pill or lozenge . . . . While the patent is silent on specific solvents, it is deemed inherent by the Examiner that in order to make a topical cream or lotion, the active ingredient would have to be dissolved in some type of solvent, and the patent describes the compound as having concentrations of from 1-5 mM and the use of acceptable carriers.

Office Action at page 2.

Independent Claims 1, 13, 15, 16, and 25 all require that the pharmaceutical composition be in the form of a "low-residue gel" or a "low-residue gel or low-residue thickened liquid." The present inventors recognized that the prior art, including the Mitchell patent cited by the Examiner, disclosed formulations that were unsuitable for administration shortly before the application of radiotherapy, as they would lead to a burning of the skin and mucous membranes in the treated area as a result of a bolus effect. *See* specification at page 2 ("These references limit the topical use of TEMPOL to formulations selected from creams, lotions, shampoos, cream rinses, and ointments. It is now recognized that these kinds of topical formulations are

unsuitable for administration shortly before the actual delivery of radiotherapy to the patient. Indeed, these product forms leave residues that can result in topical burning, including severe burns, when radiation is administered.") and page 15 ("This invention focuses on the discovery that prior art topical forms of Tempol should not be administered shortly before the actual delivery of radiotherapy to the patient. These prior art topical formulations leave a residue or film on the patient's treated area (e.g., skin, mucous membranes). If this residue or film is left on the treated area before radiotherapy, it can intensify or absorb the radiation and can cause potentially severe burning. This burning caused by the residue or film can be described as a bolus effect.").

The Mitchell reference does not contain any disclosure related to the problem of burning caused by the use of topical formulations, such as those disclosed in Mitchell, that left a residue on the patient's skin. Indeed, as noted by the Examiner, the Mitchell reference refers to topical formulations which may be "an ointment, lotion, or cream." Such formulations will, if applied shortly before the actual delivery of radiotherapy to the patient, leave a residue that will cause topical burning, as disclosed in the present specification. *See* specification at 2. Nor can the passing reference in Mitchell to a "liquid" topical formulation anticipate the "low residue gel" or "low-residue gel or low-residue thickened liquid" limitations of Claims 1, 13, 15, 16, and 25. These claims are thus not anticipated by Mitchell.

With respect to Claim 24, the Examiner states that "applying the composition topically to prevent harmful effects of radiotherapy is taught by Mitchell (*see* col. 2, lines 53-58) and evaporating solvent after applying topically is inherent since the solvents listed are volatile (methanol) and would eventually evaporate when applied to a person's skin." Office Action at page 3. Disclosure of the use a solvent may indeed inherently disclose the eventual evaporation of that solvent.

However, Claim 24 recites the steps of "evaporating solvent; and applying radiotherapy to said patient." To anticipate this claim, evaporation of the solvent in the formulation must take place before the radiotherapy is applied to the patient. Mitchell does not disclose the timing of the application of the topical formulations with respect to the application of ionizing radiation. Furthermore, as recognized by the Examiner, Mitchell is silent as to the specific solvents to be employed. *See* Office Action at page 2. It is possible that, if applied well in advance of the

application of ionizing radiation, the undisclosed solvent in the "ointment, lotion, or cream" formulation of Mitchell will evaporate before ionizing radiation is applied. However, "[i]nherency . . . may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient." *In re Robertson*, 169 F.3d 743, 745 (Fed. Cir. 1999); *see also* M.P.E.P. § 2112(IV). Rather, "the extrinsic evidence must make clear that the missing descriptive matter is necessarily present in the thing described in the reference." *In re Robertson*, 169 F.3d at 745. Because Mitchell does not disclose the timing of the application of the topical formulation, a disclosure of evaporation of the solvent before the application of ionizing radiation is not "necessarily present" in Mitchell. *Id.* For this reason, the Mitchell disclosure does not inherently anticipate Claim 24.

The remaining claims rejected over Mitchell depend from one of the independent claims described above, and contain all the limitations thereof. Because Mitchell does not anticipate the pending independent claims as amended, it cannot anticipate the claims depending from these independent claims. Accordingly, Claims 1-2, 6-10, 12-17, and 20-25 are not anticipated by Mitchell.

2. Golz-Berner, PCT Publication No. WO 99/66881 (U.S. Pat. No. 6,426,080)

The Examiner has also rejected Claims 1-9 and 11-25 under 35 U.S.C. § 102(b) as being anticipated by Golz-Berner et al., PCT Publication No. WO 99/66881 (employing U.S. Patent No. 6,426,080 as an English equivalent thereto). Applicant respectfully traverses this rejection.

The Examiner characterizes the Golz-Berner reference as teaching "a cosmetic preparation of active substances to protect the skin (including TEMPOL)." Office Action at p. 3. Applicant respectfully disagrees with the Examiner's characterization of the disclosure of the Golz-Berner reference. Golz-Berner discusses the use of Tempol and other nitroxides solely as test substances for determining the radical protection factor (RPF) of the cosmetic preparations disclosed. *See* Golz-Berner '080 at col. 7, lines 56-64. Applicant notes in this regard that none of the Examples in Golz-Berner disclose the presence of Tempol or any other nitroxide in the composition. *See* Golz-Berner '080 at col. 9, line 55 – col 12, line 27.

Golz-Berner thus does not disclose the use of a nitroxide radioprotector in the actual pharmaceutical composition, as set forth in the pending claims, but rather only as a test substance which may be added to the cosmetic compositions in order to determine their effectiveness.

Accordingly, Claims 1-9, 11-17, and 19-25, all of which require the presence of a nitroxide radioprotector in the claimed composition or use of a nitroxide radioprotector in the claimed method, are not anticipated by Golz-Berner.

Withdrawal of these rejections is respectfully requested.

Claim Rejection Under 35 U.S.C. § 103

The Examiner has rejected Claims 1-25 under 35 U.S.C. § 103(a) as being unpatentable over Mitchell et al., U.S. Patent No. 5,462,946, in view of Golz-Berner et al., PCT Publication No. WO 99/66881. Claim 18 has been canceled. Applicant traverses this rejection with respect to Claims 1-17 and 19-25.

Golz-Berner is concerned with the preparation of cosmetic preparations, with one stated objective of the invention being "to provide a preparation of active substances that keeps its radical protection potential over a long period of time." Golz-Berner at col. 1, lines 52-54. Thus, in contrast to the topical formulations of the present application, which are designed to leave little residue on the skin after a short period of time, Golz-Berner is concerned with maintaining the preparation on the skin for an extended period. This is shown by the ingredients in the various Golz-Berner exemplary cosmetic compositions, which are described as "creams," "sun gels" and "emulsion-based fluids." Applicant notes, for example, that each of these exemplary formulations contains a considerable amount of glycerine. Glycerine is highly hygroscopic and will slow the rate of evaporation of the solvents employed in the compositions. Because a significant amount of glycerine is included in each of the examples disclosed in Golz-Berner, topical formulations made following the teachings of Golz-Berner would not result in the "low-residue gels" or "low-residue thickened liquids" required by Claims 1, 13, 15, 16, and 25. Neither, given the presence of glycerine, would the resulting formulations meet the requirements of Claim 24, wherein evaporation of the solvent occurs before radiotherapy is applied. As a result, even if the teachings of Golz-Berner were combined with those of Mitchell, Claims 1-17 and 19-25, as presently amended, would not be rendered obvious.

Withdrawal of this rejection is respectfully requested.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 11-1410.

Respectfully submitted,

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